

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:) Confirmation No.: 4282
)
Kenshi KAMEI et al) Art Unit: 1614
)
Appln. No.: 10/532,585) Examiner: P.G. Spivack
)
Filing Date: October 24, 2003)
371 date: April 25, 2005) January 8, 2009
)
For: THERAPEUTIC AND/OR) ATTY.'S DOCKET: KAMEI=2
PREVENTIVE AGENT...)

REPLY TO FINAL REJECTION: FOURTH REQUEST FOR RECONSIDERATION

Honorable Commissioner for Patents
U.S. Patent and Trademark Office
Randolph Building, Mail Stop **AF**
401 Dulany Street
Alexandria, VA 22314

Sir:

Applicants hereby acknowledge receipt of the final
rejection of October 8, 2008.

Claims 10 and 15-19 remain unamended in the
application, and these claims define not only novel subject
matter, but also nonobvious subject matter. Favorable
reconsideration and allowance are again respectfully
requested.

Some progress has been made in that the rejection
based on Section 102 has been withdrawn by the PTO.
Applicants accordingly understand that the PTO now

acknowledges that applicants' claims define novel subject matter.

The rejection of the claims based on Koga under Section 103 as being obvious has been again repeated, and it is again respectfully traversed by the applicants for the reasons already of record as set forth in more than one previous reply, and hereby respectfully repeated by reference.

In the new Office Action at page 2, the examiner states, "On page 271, lines 6 to 8, Koga states GM-611 is a potential agent in the treatment of constipation". However, the corresponding description of Koga only states, "Other possible applications, including gastroesophageal reflux disease and constipation, are also being investigated", and there is no reference to specific results of any such investigation.

Therefore, at the time the present invention was made, no one could predict efficacy of GM-611 on constipation in light of the description of Koga.

Further, the rejection also states: "Koga states GM-611 is expected to have the same clinical applications as erythromycin A at the bottom of the second column on page 269." In this regard, applicants already referred to Bradette et al. (J. Gastrointest. Mot., 1993, 5, 247 to 251), Jameson et al. (Aliment Pharmacol. Ther., 1992, 6, 589 to 595) and Bassotti et al. (Z. Gastroenterol., 1998, 36, 209 to 231) in

our former response dated September 18, 2001, which three documents firmly teach away from the subject invention in connection with erythromycin. Bassotti is the same reference referred to in Koga, and it teaches contrary to what the PTO relies upon. Please note that the prior art is to be considered "as a whole."

Applicant pointed out as follows:

"In light of the prior art disclosed in these documents, a person skilled in the art would naturally have considered that GM-611 would likely have no effect on the colonic motility as the parent compound, erythromycin also has no effect, and therefore that GM-611 cannot reasonably be expected to succeed in the treatment of constipation, and thus cannot be applied to the treatment of constipation." (Page 5, second full paragraph of the Reply dated September 18, 2007)

Respectfully, the three documents as noted above and previously firmly teach away from the subject invention in connection with what they disclose and teach regarding erythromycin.

In the new Office Action, the Examiner states, "Koga teaches the administration of erythromycin increased stool frequency and decreased colonic transit time when orally administered to patients with idiopathic constipation" (page

3, 24 line from the bottom to page 4, line 1 of the Office Action).

However, Koga also states that "others reported that intravenously injected EMA failed to effectively stimulate colonic motility, except for the lowest dose investigated, in chronically constipated patients" referring to Bassotti et al. (Reference No.36) which is mentioned above (page 270, left column, lines 21 to 24 of Koga).

In addition, enclosed herewith is further evidence in the form of Nissan et al, The American Journal of Surgery 183 (2002) 413 to 418: published on April 18, 2002, which also teaches away from the present invention.

This document discloses the experimental results that the muscarinic receptor agonist carbachol evoked contraction in the gallbladder, ileum, and colonic smooth muscle of humans that were reduced by erythromycin at 10-4 M to 72% \pm 24%, 77% \pm 22% and 76% \pm 22% of control values, respectively (page 413, Abstract of the document).

Based on these results, the document states that erythromycin antagonized direct cholinergic effects on various smooth muscles from the human alimentary tract in a concentration-dependent manner, and it concludes: "The inhibitory effect of EM on gastrointestinal motility may prove beneficial in patients suffering from abnormally enhanced

gastrointestinal motility such as patients with intractable diarrhea or patients with irritable bowel syndrome." (Page 413, Abstract and page 418, left column, lines 13 to 17 of the document).

In other words, the document suggests that the effect of erythromycin (EM) inhibiting contraction of colon may be useful for treating intractable diarrhea, a teaching directly opposite to any teaching which would lead to the present invention. In light of this document, applicants firmly believe and respectfully maintain that no person skilled in the art could conceive of the application of erythromycin for treating constipation, since the document suggests that erythromycin exhibits the effect of inhibiting defecation.

It follows that if a person skilled in the art considered that GM-611 has the same clinical applications as erythromycin A, as the rejection concludes, no person skilled in the art would apply GM-611 for the treatment of constipation.

In addition to the statement regarding erythromycin, the rejection states: "Koga states previous authors have suggested the presence of motilin receptors exist on colonic smooth muscle, indicating potential therapeutic application of motilin agonists in idiopathic constipation and irritable

bowel syndrome." Enclosed are two further documents: Hasler et al, *Gastroenterology*, 1990, 98, A3581 and Chiba et al., *Aliment Pharmacol. Ther.*, 2000, 14, 955 to 960, which are referred to in Koga and correspond to the references of the previous authors.

In Hasler et al, *in vivo* experiments were conducted by using tissues of rabbit.

Chiba et al used dogs as an experimental animal, and this document only states as a conclusion that motilin receptors are apparently present in the canine small bowel and colon. In this connection, applicants had already pointed out the difference of motilin receptors among species on page 7, 8th line from the bottom to page 8, line 5 of the Reply filed September 18, 2007, referring to several documents as evidence.

In that Reply, applicants further referred to Strunz et al (*Gastroenterology*, 1975, 68, 1485 to 1491) and Jameson et al (*Aliment Pharmacol. Ther.*, 1992, 6, 589 to 595), copies of which were filed and should be of record. Strunz et al discloses that strips of circular muscle of the descending colon, sigmoid colon, sigmoid colon, and rectum, which tissues were derived from humans, proved unresponsive even to 0.5×10^{-6} g/mL of 13-norleucine motilin, which is biologically equivalent to motilin (page 1488, right column, lines 1 to 6),

while circular muscle of the descending colon which was derived from a rabbit, responded to 13 norleucine motilin at a concentration as low as 20×10^{-9} g/mL (page 1487, right column, lines 11 to 14). However, reviewing the Reply dated September 18, 2007, applicants found that they had not referred to the origin of each of the tissues used in the experiments. This omission has now been rectified above.

Further, Jameson et al describes that motilin receptors may be absent in the human colon and the therapeutic potential of erythromycin and its analogues may be limited dysmotility affecting the proximal gut only. The Examiner's attention is respectfully invited to the descriptions in these two documents, whereby it should be clear that these descriptions teach away from the present invention.

Hasler et al also discloses results of *in vivo* experiments by administering erythromycin (250 mg po quid) to 8 healthy volunteers, stating that stool frequency was increased by administration of erythromycin, while (significantly) diarrhea and abdominal pain were increased. This document also states that profound acceleration of transit was noted in 3/8 subjects, although this did not reach statistical significance. Applicants believe and respectfully submit that persons skilled in the art would understand that increased stool frequency with increased diarrhea and

abdominal pain are caused by altered bacterial flora due to overdosing of the antibiotic erythromycin.

Furthermore, the Examiner in the new action refers to Sharma et al, titled as "Effect of Oral Erythromycin on Colonic Transit in Patients with Idiopathic Constipation" (Digestive Diseases and Sciences, 1995, 40 (11), 2446 to 2449) in the new Office Action at page 3, lines 5 to 3 from the bottom. This document states that *in vivo* experiment results suggest erythromycin is of therapeutic value in patients with idiopathic constipation (page 2446, abstract, last two lines). On the other hand, the document also states that after stopping administration of erythromycin, in some patients the increase in stool frequency persisted for the next 15 days (page 2447, right column, lines 16 to 18), and this again suggests that the antibacterial effect of erythromycin contributed to the effects persisting after stopping the drug (page 2448, left column, lines 15 to 18).

Further, applicants note that the dose of erythromycin used in the experiment was very high, i.e. 1 g/day for two weeks followed by 500 mg/day for another two weeks (Page 2446, abstract, lines 5 to 6).

In light of the foregoing, applicants believe and respectfully submit that the *in vivo* results disclosed in Sharma et al should be largely attributed to the anti-bacterial effect and overdosing of erythromycin, and that no person skilled in the art would apply GM-611 to the treatment of constipation, since GM-611 has no anti-bacterial effect.

In conclusion, applicants strongly submit that a person skilled in the art who understood the material technical knowledge of the art as noted above and previously, at the time the present invention was made could not conceive of the present invention, even in light of what might be interpreted in Koga by the few comments to the contrary cited in the rejections.

Furthermore, applicants believe and respectfully maintain the Reply dated September 18, 2008, already provided what the Examiner points out in the present Office Action is needed. Namely, applicants already submitted plural prior art documents that teach away from the subject invention, and the Examiner stated in the Office Action dated December 12, 2007, that "Applicants' argument in response to the rejection set forth in the last Office Action is persuasive."

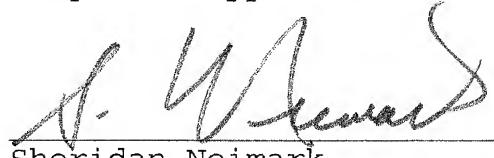
Appn. No. 10/532,585
Amd. dated January 8, 2009
Reply to Office Action dated October 8, 2008

The prior art "as a whole" teaches away from the present invention. Withdrawal of the rejection is respectfully requested.

Respectfully submitted,

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